UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF

PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE:June 14, 2001

SUBJECT: LINDANE- Responses to registrant's error corrections and comments

FROM: Suhair Shallal, Ph.D.
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THRU: Susan Hummel, Branch Senior Scientist
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Special Review and Reregistration Division

DP Barcode: D274519
Case: 818566
Submission: S596448
Chemical: Lindane
PC Code: 009001
Registrant: CIEL

ACTION REQUESTED : To respond to errors, corrections and comments raised by the registrant regarding the Lindane RED document.

RESPONSE: The following are responses to the comments on individual discipline chapters (chemistry/dietary, toxicology, occupational/residential exposure) and the Reregistration Eligibility Document (RED) by subject manner as they appeared in the registrant's memo:

Assessment (RED) and Toxicology Chapter:

C Carcinogenicity

The Cancer Assessment Review Committee (CARC) is scheduled to evaluated the newly submitted mouse carcinogenicity study as well as other submitted and published studies which are relevant to the carcinogenicity issue of lindane.

C Dermal Absorption

The Feldman and Maibach (1974) study uses human data to arrive at its conclusions for dermal absorption values; for lindane, it is approximately 10%. It does not rely upon animal studies for its findings. The dermal absorption study in rats (MRID 40056107) suggests that 18 % is a reasonable approximation of dermal absorption in rats.

C Developmental neurotoxicity

With the submission of the positive control data the Developmental Neurotoxicity study (MRID 45073501) has been upgraded to Acceptable/Guideline.

C Subchronic Inhalation Study

HED concurs with the registrant that the original NOAEL of 0.1 mg/m^3 (0.025 mg/kg/day) based on kidney lesions and increased kidney weight in males at 0.5 mg/m^3 (0.13 mg/kg/day) should be changed. These effects are associated with the accumulation of alpha 2µ globulin and are not relevant for human risk assessment. The NOAEL in the subchronic inhalation study (MRID 00255003) has been revised and now reflects the new NOAEL of 0.5 mg/m^3 (0.13 mg/kg/day) based on increased kidney weights in females and bone marrow effects at 5.0 mg/m^3 (HIARC, 5/2001). These changes will also be incorporated in the revisions of the Occupational risk assessment associated with inhalation exposure if applicable.

C Renal and Hepatic Toxicity

Studies that show effects on the liver and kidneys include the following: In addition to periancinar hepatocyte hypertrophy in males and females at the two highest doses in a chronic toxicity/carcinogenicity study in rats (MRID 42891201), there was an increased kidney weights in female rats in the subchronic inhalation toxicity study (MRID 00255003) and induction of liver tumors in mice (Wolff et al 1987, Thorpe and Walker 1973). Accounts in the published literature also indicate that changes in cellular permeability and the generation of superoxide radicals coupled with decreased superoxide dismutase (SOD) activity may contribute to the toxicity seen in the kidney and liver (Arisi et al, Junqueira et al, Lu et al, Perocco et al, Videla et al).

C Endocrine Disruptor Considerations

In numerous published studies have implicated lindane in the disruption and modulation of estrogen and testosterone function (Chowdhury et al, Dalsenter et al, Li et al, Ronco et al, Silverstroni et al, Suwalsky et al). Testicular atrophy, disruption of spermatogenesis, inhibition of estradiol-receptor complex formation, and reduced ovulation rate are some of the effects seen after administration of lindane to rats or rabbits. The Environmental Fate and Effects Division outlined some of the effects seen in fish and wildlife in their reregistration eligibility document. The statement made in the Toxicology Chapter clearly concedes that further studies are needed to establish if a risk to human health exists.

C FQPA Safety Factor Considerations

The registrant's contention that the effects seen in the Developmental Neurotoxicity Study (MRID 45073501) and the Reproductive Toxicity Study (MRID 42246101) can be attributed to the transfer of lindane via mother's milk may or may not be valid. This, however, does not discount the increase in susceptibility to pups, since the pups are the sole recipients of this source of lindane. Additionally, lindane has also been shown to be transferred to fetuses via the placenta (Khanna et al, Pompa et al). Exposure can therefore occur both pre- and post-natal; these facts increase rather than diminish the requirement for an additional safety factor.

Occupational and Residential Exposure Assessment:

The dermal absorption factor (10%) currently cited in the Preliminary Risk Assessment is deemed to be relevant to humans as discussed above. The NOAEL in the subchronic inhalation study (MRID 00255003) has been revised and now reflects the new NOAEL of 0.5 mg/m^3 based on increased kidney weights in females and bone marrow effects at 5.0 mg/m^3 . Other comments in this section are addressed in the attached memorandum (D. Jaquith, 6/5/2001, D275419).

Product and Residue Chemistry Chapters

HED's Response to the Registrant's Comments on the Lindane Product and Residue Chemistry Chapter.

4.2 GLN 860.1300: Nature of the Residue - Plants

New Nature of the Residue Studies are required as stated in the memorandum (D272625, T. Morton, 2/13/01). Following are the conclusions from this memorandum:

C For HED to consider using the literature study referenced in the waiver request, CIEL must obtain the raw data from the wheat metabolism study and make it available for audit.

C In addition, metabolism data for wheat forage, storage intervals and conditions, and details on metabolite identification are required to be submitted.

- A metabolism study on a representative leafy vegetable and radish is required.

- The Agency will not require the new metabolism studies to be conducted at exaggerated application rates. However, all labels must be amended to reflect a maximum rate no higher than the rate tested.

4.3 GLN 860.1300: Nature of the Residue - Animals

The Revised Lindane Product and Residue Chemistry Chapter will state the nature of the residue in ruminants is now adequately understood. Data which were submitted by the registrant and reviewed by HED after the completion of the Lindane Product and Residue Chemistry Chapter will be incorporated.

4.4 GLN 860.1340: Residue Analytical Methods

The ChemSAC met on 5/23/2001 and concluded that the radiovalidation requirement stands since the confined rotational crop study was inadequate. Since that study was inadequate, it could not be used to fulfill the radiovalidation requirement for the method.

4.6 GLN 860.1380: Storage Stability Data

Storage stability data for wheat grain, wheat hay, and wheat straw were submitted by the registrant and reviewed by HED (D274313, T. Morton, 5/10/01) and will be incorporated into the Revised Lindane Product and Residue Chemistry Chapter. Also HED will translate corn data to sorghum and mustard data to radish tops. This will be incorporated into the Revised Lindane Product and Residue Chemistry Chapter. However, additional data may be required if metabolites other than lindane, per se, are determined to be residues of concern.

4.7 GLN 860.1500: Crop Field Trials

Mustard data will be translated to radish tops, therefore, no residue data will be required for radish tops. Also, corn forage and stover data will be translated to sorghum forage and stover. No residue data will be required for sorghum forage and stover. However, additional data may be required if metabolites other than lindane per se are determined to be residues of concern.

4.8 GLN 860.1520: Processed Food/Feed

In a memorandum from S. Funk to D. Edwards (dated 8/1/96), S. Funk states in Conclusion 1: "A processing study has not been conducted, and residues as great as 0.12 ppm could occur in corn oil. Corn with quantifiable residues of lindane must be processed into the commodities indicated in.....". The theoretical maximum concentration factor for corn oil is 25X while the theoretical maximum concentration factor for canola oil is 3.0X. Therefore, a processing study on corn is still required. However, additional data may be required if metabolites other than lindane per se are determined to be residues of concern.

HED Responses in regard to the Dietary Exposure Analysis

A revised Dietary Exposure Analysis (T. Morton, 5/30/2001, D274825) is attached to this memo.

References

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